A SURVEY ON 4D INTRACARDIAC ULTRASOUND VECTOR FLOW IMAGING

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Abstract—Magnetic resonance imaging (MRI) has become an important tool for the clinical evaluation of patients with cardiovascular disease. Since its introduction in the late 1980s, 2-dimensional phase contrast MRI (2D PC-MRI) has become a routine part of standard-of-care cardiac MRI for the assessment of regional blood flow in the heart and great vessels. More recently, time-resolved PC-MRI with velocity encoding along all three flow directions and three-dimensional (3D) anatomic coverage (also termed '4D flow MRI') has been developed and applied for the evaluation of cardiovascular hemodynamics in multiple regions of the human body. 4D flow MRI allows for the comprehensive evaluation of complex blood flow patterns by 3D blood flow visualization and flexible retrospective quantification of flow parameters. In vivo characterization of intracardiac blood velocity vector fields may provide new clinical information, but is currently not available for bedside evaluation. In this work, 4D vector flow imaging for intracardiac flow assessment is demonstrated using a clinical ultrasound (US) system and a matrix array transducer, without the use of contrast agent. Two acquisition schemes were developed, one for full volumetric coverage of the left ventricle at 50 volumes per second (vps), and a 3D thick-slice setup with continuous frame acquisition (4000 vps), both utilizing ECG-gating. The 3D vector velocity estimates were obtained using a novel method combining phase and envelope information. In vitro validation in a rotating tissue-mimicking phantom revealed velocity estimates in compliance with the ground truth, with a linear regression slope of 0:80, 0:77, and 1:03 for the x, y and z velocity components, and standard deviations of 2:53, 3:19, and 0:95 cm/s, respectively. In vivo measurements in a healthy left ventricle showed good agreement with PC-MRI. Quantitative analysis of energy loss (EL) and kinetic energy (KE) further showed similar trends, with peak KE at 1:5 and 2:4 mJ during systole and 3:6 and 3:1 mJ for diastole for US and PCMRI. Similar for EL, 0:15, 0:2 and 0:7 mW was found during systole, and 0:6 and 0:7 mW during diastole, for US and PCMRI respectively. Overall, a potential for ultrasound as a future modality for 4D cardiac vector flow imaging was demonstrated, which will be further evaluated in clinical studies.

Index Terms—blood flow imaging, intracardiac flow imaging, plane wave imaging, vector flow imaging, 4D ultrasound.

I. INTRODUCTION

MR imaging is widely accepted by clinicians as a valuable tool for diagnosing cardiac and vascular diseases, measuring disease severity and assessing patient response to medical and surgical therapy. The technique has been further developed over the last few decades to provide not only morphological information on cardiovascular anatomy, but also functional information on cardiac perfusion, myocardial viability, and blood flow. This functional information may allow a more thorough assessment of cardiovascular diseases. Since its original description in the 1980s (1-4), phase contrast (PC) magnetic resonance imaging (MRI) has seen broad clinical acceptance for the visualization and quantitative evaluation of blood flow in the heart, aorta and large vessels (5-7). Further development of PC techniques have allowed for the acquisition of a time-resolved (CINE), three-dimensional (3D) PC-MRI with three-directional velocity encoding which is often referred to as "4D flow MRI". In contrast to standard 2D CINE PC-MRI which allows for the evaluation of blood flow in a single user selected 2D slice, 4D flows MRI can provide information on the temporal and spatial evolution of 3D blood flow with full volumetric coverage of any cardiac or vascular region of interest. A particular advantage over 2D CINE PC-MRI is related to the possibility for retrospective selection of territories at any location inside the 3D data volume to perform post-hoc quantification of blood flow parameters such as total flow, peak velocity or regurgitate fraction (8-12). Moreover, the combination of 3D blood flow visualization with flow quantification enables a new and previously unfeasible comprehensive evaluation of the impact of cardiovascular pathologies on global and local changes in cardiac or vascular hemodynamics (13-19). A number of 4D flow MRI studies have attempted to assess and corroborate blood flow parameters associated with clinical markers commonly measured with Doppler ultrasound (US) and echocardiography: peak pressure gradient ($r=0.96$, $P<0.05$) (20), peak and mean velocities ($r=0.83$ and $r=0.76$, respectively) (21), net flow over the cardiac cycle, vessel area, etc. However, 4D flow MRI can also provide the opportunity

to improve upon current clinical hemodynamic assessments by deriving additional metrics of cardiovascular hemodynamics. A number of groups have shown that 4D flow MRI can be used to derive advanced hemodynamic measures such as wall shear stress (WSS) (22-24), pressure difference (20,25-27), pulse wave velocity (28,29), turbulent kinetic energy (TKE) and others (30,31) for an improved characterization of cardiovascular disease beyond simple measures of flow. The purpose of this review is to provide a brief introduction to the imaging techniques used to acquire 4D flow MRI data as well as the analysis tools currently used for blood flow visualization and flow quantification. Furthermore, a selected number of clinical applications will be presented to illustrate the potential of 4D flow MRI for an improved and more comprehensive evaluation of cardiovascular disease.

1.1 Background

PC MRI (also sometimes termed 'flow-sensitive MRI' or 'MR velocity mapping') takes advantage of the direct relationship between blood flow velocity and the phase of the MR signal that is acquired during a MRI measurement. To eliminate unwanted background phase effects, two acquisitions with different velocity-dependent signal phase are typically needed to encode (using bipolar magnetic field gradients) and measure blood flow velocity along a single direction (5, 32, and 33). Subtracting of phase images from the two acquisitions removes background phase effects. The signal intensities in the resulting phase difference images are directly related to the blood flow velocity and can thus be used to visualize and quantify blood flow (PC principle). For cardiovascular applications, the 2D PC data is acquired over multiple cardiac cycles using ECG gated CINE imaging to measure time-resolved pulsatile blood flow as illustrated in Figure 1. For a standard 2D CINE PC-MRI clinical protocol, the 2D imaging slice is usually positioned normal to the vessel lumen. Data acquisition typically includes single-direction velocity measurement orthogonal to the 2D imaging slice (through-plane encoding) and is performed during a 10-20-second breath hold period. For certain patients, e.g., patients with congestive heart failure and shortness of breath, this length of breath-hold may not be possible, and is a potential limitation of the clinical implementation of cardiovascular MR. Following image reconstruction, 2D CINE PC-MRI yields a series of anatomical (magnitude) and flow velocity (phase difference) images that represent the temporal changes of morphology and blood flow over the cardiac cycle. Typical measurement parameters are: spatial resolution, 1.5-2.5 mm; temporal resolution, 30-60 ms; slice thickness, 5-8 mm.

1.2 Motivation

An important (user-defined) PC-MRI parameter is the Venc, which represents the maximum flow velocity that can be acquired (Figure 1). As shown in Figure 2, when the underlying velocity exceeds the acquisition setting for Venc, velocity aliasing can occur which is typically visible as a sudden change from high to low velocity within a region of flow. If aliasing artifacts are present, accurate flow visualization and quantification may be compromised unless antialiasing correction can be successfully performed (34). Alternatively, the Venc can be increased and the acquisition is repeated to avoid aliasing. It is important to note, however, that velocity noise is directly related to the Venc (5). Therefore, selecting a high Venc may alleviate the issue of velocity aliasing but will also increase the level of velocity noise in flow velocity images. As a result, the Venc should ideally be selected as high as needed to avoid aliasing but as low as possible to reduce velocity noise. As a general rule, to capture the best image quality, the chosen Venc should represent the physiological velocity of the vessel of interest and be adapted to the measurement of interest and present hemodynamic conditions.

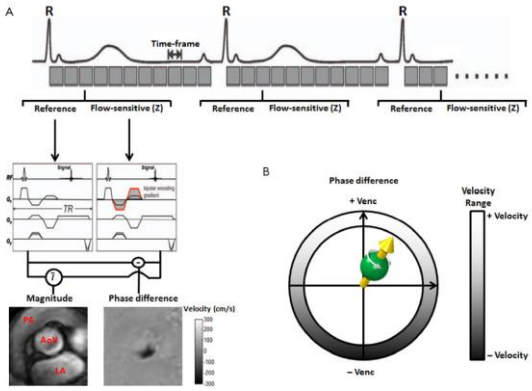

Figure 1 Standard 2D CINE PC-MRI with one-directional through-plane (Z) velocity encoding. (A) Data acquisition is synchronized with the RR-interval by ECG gating.

II. LITERATURE SURVEY

Sophia Houriez et al. compare various methods of transit time (TT) and consequently aortic Pulse Wave Velocity (aoPWV) estimation from 4D MRI (aoPWV=aortic length/TT), in terms of associations with age and Bram well-Hill (BH aoPWV). Method: We studied 43 healthy subjects (48±17yrs.) who had aortic 4DFlow MRI. Three strategies were used to estimate aoPWV: (S1) using flow curves in two aortic locations to calculate TT (ascending (AA) and distal descending aorta (dDA)) as a 2D-like strategy, (S2 and S3) using flow curves of the entire aortic path-line between dDA and AA to estimate TT with various methods: cross-correlation; Fourier and Wavelet or aoPWV by fitting a plan on the systolic upslope of flow curves. Results: Expected associations with age were found for the three strategies with

strongest correlations for 3D-like strategies than 2D-like strategy (S2:r=0.75, S3:r=0.72,p<0.001, S1: r=0.55,p<0.001). Similar results were found for associations with BH aoPWV. Best results were obtained using the TT wavelet based approach. Conclusion: Low temporal resolution of 4DFlow is compensated by aortic 3D coverage, leading to strong associations of aoPWV with age and BH aoPWV.

Ali Bakhshinejad et al. Time resolved phase-contrast magnetic resonance imaging 4D-PCMR (also called 4D Flow MRI) data while capable of non-invasively measuring blood velocities, can be acted by acquisition noise, low artifacts, and resolution limits. In this paper, we present a novel method for merging 4D Flows MRI with computational fluid dynamics (CFD) to address these limitations and to reconstruct de-noised, divergence-free high-resolution lowest. Proper orthogonal decomposition (POD) is used to construct the orthonormal basis of the local sampling of the space of all possible solutions to the low equations both at the low-resolution level of the 4D Flow MRI grid and the high-level resolution of the CFD mesh. Low-resolution, de-noised low is obtained by projecting in-vivo 4D Flows MRI data onto the low-resolution basis vectors. Ridge regression is then used to reconstruct high-resolution de-noised divergence-free solution. The elects of 4 D Flow MRI grid resolution and noise levels on the resulting velocity eldest are further investigated. A numerical phantom of the low through a cerebral aneurysm was used to compare the results obtained using the POD method with those obtained with the state-of-the-art de-noising methods. At the 4D Flow MRI grid resolution, the POD method was shown to preserve the small low structures better than the other methods, while eliminating noise. Furthermore, the method was shown to successfully reconstruct details at the CFD mesh resolution not discernible at the 4 D Flow MRI grid resolutions. This method will improve the accuracy of the clinically relevant derived parameters, such as pressure gradients and wall shear stresses, computed from in-vivo 4D Flow MRI data.

Silvia Born et al. Four-dimensional MRI is an in vivo flow imaging modality that is expected to significantly enhance the understanding of cardiovascular diseases. Among other fields, 4D MRI provides valuable data for the research of cardiac blood flow and with that the development, diagnosis, and treatment of various cardiac pathologies. However, to gain insights from larger research studies or to apply 4D MRI in the clinical routine later on, analysis techniques become necessary that allow to robustly identifying important flow characteristics without demanding too much time and expert knowledge. Heart muscle contractions and the particular complexity of the flow in the heart imply further challenges when analyzing cardiac blood flow. Working toward the goal of simplifying the analysis of 4D MRI heart data, we present a visual analysis method using line predicates. With line predicates recalculated integral lines are sorted into bundles with similar flow properties, such as velocity, vortices, or flow paths. The user can combine the line predicates flexibly and by that carve out interesting flow features helping to gain overview. We applied our analysis technique to 4D MRI data of healthy and pathological hearts and present several flow aspects that could not be shown with current methods. Three 4D MRI experts gave feedback and confirmed the additional benefit of our method for their understanding of cardiac blood flow.

Anthony G et al. Magnetic resonance imaging (MRI) has long been recognized as a powerful tool for cardiovascular imaging because of its unique potential to measure blood flow, cardiac wall motion and tissue properties jointly. However, many clinical applications of cardiac MRI have been limited by low imaging speed. Three-dimensional cardiovascular MRI in real-time, or 4D cardiovascular MRI without cardiac and respiratory gating or triggering, remains an important technological goal of the MR cardiovascular research community. In this paper, we present a novel technique to achieve 4D cardiovascular MR imaging in unprecedented spatiotemporal resolution. This breakthrough is made possible through a creative use of sparse sampling theory and parallel imaging with phased array coils and a novel implementation of data acquisition and image reconstruction. We have successfully used the technique to perform 4D cardiovascular imaging on rats, achieving 0.65 mm × 0.65 mm × 0.31 mm spatial resolution with a frame rate of 67 fps. This capability enables simultaneous imaging of cardiac motion, respiratory motion, and first-pass myocardial perfusion. This in turn allows multiple cardiac assessments including measurement of ejection fraction, cardiac output, and myocardial blood flow in a single experiment. We believe that the proposed technique can open up many important applications of cardiovascular imaging and have significant impact on the field.

Petter Dyverfeldt et al. Pulsatile blood flow through the cavities of the heart and great vessels is time-varying and multidirectional. Access to all regions, phases and directions of cardiovascular flows has formerly been limited. Four-dimensional (4D) flow cardiovascular magnetic resonance (CMR) has enabled more comprehensive access to such flows, with typical spatial resolution of 1.5×1.5×1.5 – 3×3×3 mm3, typical temporal resolution of 30-40 ms, and acquisition times in the order of 5 to 25 min. This consensus paper is the work of physicists, physicians and biomedical engineers, active in the development and implementation of 4D Flows CMR, who have repeatedly met to share experience and ideas. The paper aims to assist understanding of acquisition and analysis methods, and their potential clinical applications with a focus

on the heart and greater vessels. We describe that 4D Flow CMR can be clinically advantageous because placement of a single acquisition volume is straightforward and enables flow through any plane across it to be calculated retrospectively and with good accuracy. We also specify research and development goals that have yet to be satisfactorily achieved. Derived flow parameters, generally needing further development or validation for clinical use, include measurements of wall shear stress, pressure difference, turbulent kinetic energy, and intracardiac flow components. The dependence of measurement accuracy on acquisition parameters is considered, as are the uses of different visualization strategies for appropriate representation of time-varying multidirectional flow fields. Finally, we offer suggestions for more consistent, user-friendly implementation of 4D Flows CMR acquisition and data handling with a view to multicenter studies and more widespread adoption of the approach in routine clinical investigations.

Morgane Evin et al. Left atrium (LA) is a principal site of thrombus formation inducing thromboembolic events, which have been associated with LA low flow velocities. Recent developments in magnetic resonance imaging (MRI) 4D flow analysis enable a non-invasive visualization of LA flow patterns. Our main objective was to investigate modifications of the main vortices in the LA with regards to LA functional indices in 4 patients with atrial fibrillation (AF) and 6 healthy volunteers. Vortices threshold and Q-criterion indices were computed from the centered vortices calculation on filtered 4D velocity MRI images. Phasic LA longitudinal strains were computed on cine MRI images using LA feature tracking algorithm. LA dilation in AF came along with a drop in LA longitudinal strains. Best correlations between LA flow and functional changes were found for velocity vs. longitudinal strains corresponding to reservoir and LA contraction phases ($r=0.69$ and $r=0.81$, $p<0.03$). Similarly, the highest correlation was found during LA contraction phase for associations between LA longitudinal strains and Q-criterion ($r=0.52$). In AF, LA functional changes are tightly associated with flow disorganization during the cardiac cycle especially during LA contraction phase.

F Ong et al. 4D flows MRI is a promising method for providing global quantification of cardiac flow in a single acquisition, yet its use in clinical application suffers from low velocity-to-noise ratio. In this work, we present a novel noise reduction processing for 4D flow MRI data using divergence-free wavelet transform. Divergence-free wavelets have the advantage of enforcing soft divergence-free conditions when discretization and partial valuing result in numerical non-divergence-free components and at the same time, provide sparse representation of flow in a generally divergence-free field. Efficient denoising is achieved by appropriate shrinkage of divergence free and non-divergence-free wavelet coefficients. To verify its performance, divergence-free wavelet denoising was performed on simulated flow and compared with existing methods. The proposed processing was also applied on in vivo data and was demonstrated to improve visualization of flow data while preserving quantifications of flow data.

Susanne Schnell et al. Purpose of review to evaluate the feasibility of 4-dimensional (4D) flow MRI for the clinical assessment of cerebral and extra cerebral vascular hemodynamics in patients with neurovascular disease. Recent findings 4D flow MRI has been applied in multiple studies to qualitatively and quantitatively study intracranial aneurysm blood flow for potential risk stratification and to assess treatment efficacy of various neurovascular lesions, including intraaneurysmal and parent artery blood flow after flow diverter stent placement and staged embolization's of arteriovenous malformations and vein of Galen aneurysmal malformations. Recently, the technique has been utilized to characterize age-related changes of normal cerebral hemodynamics in healthy individuals over a broad age range. Summary 4D flow MRI is a useful tool for the noninvasive, volumetric and quantitative hemodynamic assessment of neurovascular disease without the need for gadolinium contrast agents. Further improvements are warranted to overcome technical limitations before broader clinical implementation. Current developments, such as advanced acceleration techniques (parallel imaging and compressed sensing) for faster data acquisition, dual or multiple velocity encoding strategies for more accurate arterial and venous flow quantification, ultrahigh-field strengths to achieve higher spatial resolution and streamlined post processing workflow for more efficient and standardized flow analysis, are promising advancements in 4D flow MRI.

Aiqi Sun et al. Conventional phase-contrast (PC) MRI relies on electro- cardiogram (ECG)-synchronized cine acquisition and respiration control. It often results in relatively low data acquisition efficiency, and is unable to assess blood flow variability's. Real-time imaging is a promising technique to overcome these limitations; however, it results in a challenging image reconstruction problem with highly-under sampled (**k**; t)- space data. This paper presents a novel model-based imaging method, which integrates low-rank modeling with parallel imaging, to enable 4D real-time PC MRI without ECG gating and respiration control. The proposed method achieves an isotropic spatial resolution of 2.4 mm and temporal resolution of 35.2 ms, with three directional flow encodings. Moreover, it is able to resolve beat-by-beat flow variations, which cannot be achieved by the conventional cine-based approach. The proposed method was evaluated with in vivo experiments with one healthy subject and one

arrhythmic patient. For the first time, we demonstrate the feasibility of 4D real-time PC MRI.

Morten Smedsrud Wigen et al. In vivo characterization of intracardiac blood velocity vector fields may provide new clinical information, but is currently not available for bedside evaluation. In this work, 4D vector flow imaging for intracardiac flow assessment is demonstrated using a clinical ultrasound (US) system and a matrix array transducer, without the use of contrast agent. Two acquisition schemes were developed, one for full volumetric coverage of the left ventricle at 50 volumes per second (vps), and a 3D thick-slice setup with continuous frame acquisition (4000 vps), both utilizing ECG-gating. The 3D vector velocity estimates were obtained using a novel method combining phase and envelope information. In vitro validation in a rotating tissue-mimicking phantom revealed velocity estimates in compliance with the ground truth, with a linear regression slope of 0:80, 0:77, and 1:03 for the x, y and z velocity components, and standard deviations of 2:53, 3:19, and 0:95 cm/s, respectively. In vivo measurements in a healthy left ventricle showed good agreement with PC-MRI. Quantitative analysis of energy loss (EL) and kinetic energy (KE) further showed similar trends, with peak KE at 1:5 and 2:4 mJ during systole and 3:6 and 3:1 mJ for diastole for US and PCMRI. Similar for EL, 0:15 -0:2 and 0:7 mW was found during systole, and 0:6 and 0:7 mW during diastole, for US and PCMRI respectively. Overall, a potential for ultrasound as a future modality for 4D cardiac vector flow imaging was demonstrated, which will be further evaluated in clinical studies.

III. CONCEPTUAL BACKGROUND

1. 4D flow MRI

In 4D flow MRI, velocity is encoded along all three spatial dimensions throughout the cardiac cycle, thus providing a time-resolved 3D velocity field (5, 35, 36). As described above, quantitative velocity measurements require two acquisitions and a subtraction for one-directional velocity encoding. Three-directional velocity measurements can be efficiently achieved by interleaved four-point velocity encoding which acquires one reference image and three velocity-encoded images along three orthogonal (x, y, z) directions (32,37,38). As for 2D CINE PC-MRI, data acquisition is synchronized with the cardiac cycle and data collection is distributed over multiple cardiac cycles using

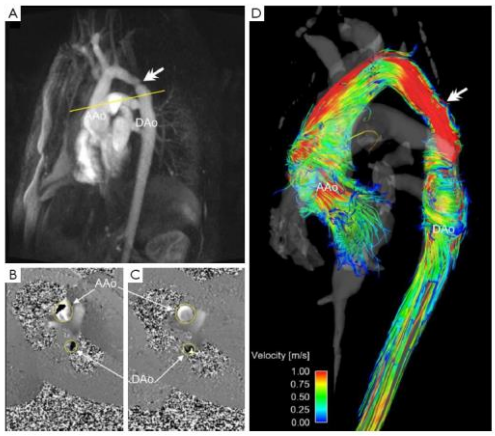

Figure 2 (A-C) 2D CINE PC-MRI with aliasing in a patient with bicuspid aortic valve disease and aortic coarctation.

After completion of the 4D flow acquisition, four time-resolved (CINE) 3D datasets are generated ('magnitude' data depicting anatomy and three flow datasets representing velocities 'Vx, Vy, and Vz'). For a schematic illustration of the data acquisition process see Figure 3. Due to the large amount of data that has to be collected (three spatial dimensions, three velocity directions, time over the cardiac cycle), efficient data acquisition is necessary to achieve practical scan times for 4D flow MRI in clinical applications. Several recent developments have allowed for marked scan time reductions. From a hardware point of view, the availability of high performance gradients has reduced both the echo and repetition times TE and TR and thereby total scan time. The introductions of phased-array coils, multi-receiver channels, and parallel imaging technology have also been applied to PC-MRI, primarily to reduce the scan time. Other methodological improvements include the use of advanced accelerated imaging approaches such as radial under sampling, kt-BLAST, kt-SENSE, kt-GRAPPA, or compressed sensing (39-42). For typical cardiovascular applications, scan times between 5 and 20 minutes can be achieved depending on heart rate, spatio-temporal resolution and anatomic

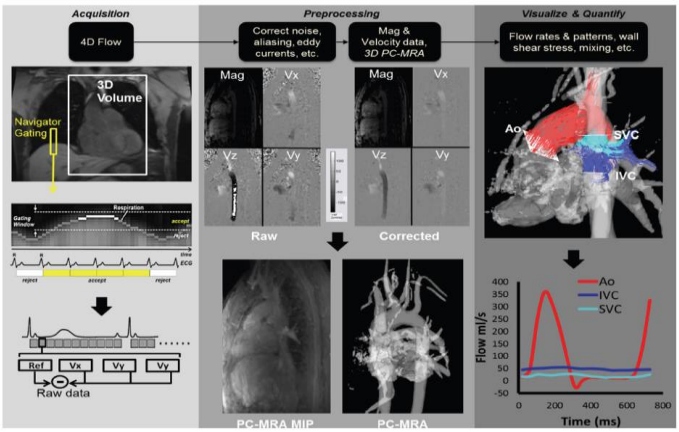

Figure 3 Data acquisition and analysis workflow for 4D flow MRI. (Left) 4D flow MRI data covering the whole heart (white rectangle) is acquired using ECG gating and respiratory control using diaphragm navigator gating.

For thoracic and abdominal applications, respiration control is thus needed to minimize breathing artifacts. Different strategies including respiratory bellows, navigator gating (see Figure 3) or self-gating techniques have been applied (43-45). An alternative technique that is increasingly used to accelerate 4D flow MRI is radial data sampling combined with under sampling [e.g., PC-VIPR, vastly under sampled isotropic projection reconstruction (46)]. Radial acquisition schemes have been shown to permit 4D flow imaging with improved scan time while providing large spherical volumetric coverage with high spatial resolution. Furthermore, PC-VIPR can reduce the occurrence of motion artifacts and enable self-gating due to intrinsic properties of radial data acquisition strategies (47).

IV. CONCLUSIONS

In vivo intra-cardiac 4D ultrasound vector flow imaging was demonstrated, and showed good correspondence when compared to PC-MRI using both quantitative and qualitative analysis. The 4D ultrasound data was acquired non-invasively and without the use of contrast agents, using a modified clinical system providing real-time color flow imaging during acquisition. An optimized hybrid 3D velocity estimator combining dealiased Doppler estimation with lateral blood speckle tracking rendered the processing pipeline bedside applicable. While demonstrating the potential of 4D ultrasound vector flow imaging, clinical feasibility requires further evaluation.

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